IN REPLYING, ADDRESS THE
ADDICTION RESEARCH CENTER
NATIONAL INSTITUTES OF MENTAL HEALTH
U. S. PUBLIC HEALTH SERVICE HOSPITAL
BOX 2000
LEXINGTON, KENTUCKY

24 January 1956

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I am attaching for your information copy of a request to the Office of Naval Research for renewal of our project here. In the event the ONR feels the project should be continued I will arrange to have the business office of the National Institutes of Health send this on at the proper time, later in the spring.

You will notice that the amount of money requested is somewhat greater than in previous years. This is necessary in order to provide funds to cover the increase in Civil Service pay which went into effect in March 1955.

You have, no doubt, by now received a copy of my letter to Dr. Pogge of The Wm. S. Merrill Company concerning efforts to reverse the LSD reaction with Frenquel. This experiment was undertaken for two reasons: (1) we had received persistent reports from other laboratories that large doses of Frenquel would ameliorate the LSD reaction, and (2) because the company claimed that in our original blocking experiment the degree of mental effect was not sufficient for the effects of Frenquel to be evident. As you see from the data in the letter, this reversal experiment was a complete failure. We were unable to distinguish Frenquel injections from placebo injections.

COMBINATIONS OF HYOSCINE AND LSD

These experiments were carried out in an attempt to determine whether Hyoscine would ameliorate or enhance the LSD reaction. Two series of experiments were done. In the first series 11 negro subjects received in randomized order Hyoscine placebo plus LSD placebo; Hyoscine placebo plus LSD; 0.42 mg. of Hyoscine plus LSD placebo; 0.42 mg. Hyoscine plus LSD; 0.64 mg. Hyoscine plus LSD; 0.85 mg. Hyoscine plus LSD. Both Hyoscine

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and LSD were given orally under "blind" conditions. The dose of LSD was 60 micrograms. Measurements were those described in previous reports.

Results are shown in left side of table. You will note that 0.64 mg. and 0.84 mg. of Hyoscine increased pupillary dilatation seen after LSD, reduced blood pressure response, increased the number of positive answers, and increased the clinical grade of reaction, but the last was not significant as compared with Hyoscine placebo and LSD.

In the second series of experiments 12 subjects were used and received in randomized order: Hyoscine placebo plus LSD placebo; Hyoscine placebo plus LSD; 1.3 mg. Hyoscine plus LSD placebo; and 1.3 mg. Hyoscine plus LSD. Results were similar but more marked with lower doses of Hyoscine than in the first series. There was marked increase in pupillary dilatation, marked decrease in blood pressure response, marked enhancement in the number of positive questions, and an increase in the clinical grade of reaction which, however, was not statistically significant.

In this last series of experiments the side effects of Hyoscine were very prominent and included sensations of giddiness and dizziness, marked blurring of vision, marked dryness of mouth, absence of perspiration, and slight confusion. It was very easy to see that the patients had both LSD and Hyoscine effects. Impression was that of a combination of drug toxicities rather than of any specific enhancement of the LSD reaction. The Hyoscine side effects probably make use of this combination impractical.

DL AMPHETAMINE AND LSD

These experiments were carried out because Hoch has stated that methamphetamine ameliorates the LSD reaction and also because of a theoretical consideration advanced by Dr. Wikler. Eleven subjects were used and received in randomized order: dl-amphetamine placebo plus LSD placebo; dl-amphetamine placebo plus LSD; dl-amphetamine plus LSD placebo; and dl-amphetamine plus LSD. Both drugs were given orally. The dose of amphetamine was 20 mg. and the dose of LSD was 60 micrograms. Dl-amphetamine was given one hour prior to LSD to provide time for dl-amphetamine effects to develop. Results are shown in the table. The only significant change with the combination as compared with LSD alone was increase in the blood pressure response. Effects with this dose of dl-amphetamine alone in our subjects, however,

were mild and the work really needs repetition, either using large doses of dl-amphetamine or some more potent sympathomimetic amine, such as dextroamphetamine, in doses sufficient to induce a more definite reaction in our patients.

RESERPINE AND LSD

The experiments previously reported have been amplified using larger amounts of Reserpine. It was felt that this work is important because of reports by Brodie, Himwich, Wooley and others on the possible relationships between LSD, Serotonin, and release of Serotonin by Reserpine. In these new experiments 12 negro subjects received in random balanced order: Reserpine placebo plus LSD placebo; Reserpine 5 mg. orally plus LSD placebo; Reserpine placebo plus LSD; Reserpine 5 mg. orally plus LSD; Reserpine 7.5 mg. orally plus LSD; Reserpine 6 mg. orally plus LSD. Dosage times are shown in the table. It is evident that there was no blocking of the LSD effect on any of our measurements.

The most interesting observation was that the patients seemed to be worse when they received 7.5 mg. of Reserpine orally or 6 mg. intramuscularly plus LSD. The intensification of the reaction was most prominent in the group that received Reserpine intramuscularly. In both these groups, patients developed tremors and ankle clonus. Mentally, nervousness, confusion, apprehension, and more frequent and more vivid hallucinations were reported. These changes are not apparent in the figures in the table because our methods of measurement are not adequate to reveal them. In rating knee jerks, nothing is allowed for tremors or for clonus. In assigning clinical grades, no allowance is made for the intensity of symptoms. At the present time we are unable to determine whether the increase represents a specific enhancement of the LSD reaction by Reserpine, or represents merely a combination of two drug toxicities.

We feel that this observation has great theoretical importance and may possibly have some practical use. We plan: (1) to attempt to establish the deleterous effect of Reserpine on the LSD reaction firmly by studying the effect of Reserpine combined with minimal doses of LSD, (2) to develop rating systems which will allow for the neurological changes and alterations in intensity and quality of symptoms, (3) if we can, firmly establish that Reserpine makes the LSD reaction worse, and study the effects of Reserpine on tolerance to LSD.

BUFOTENINE

No effects have been observed with doses of 10 mg. of this substance orally. We have now been giving the drug intramuscularly and have gradually increased the dose to 15 mg. Mild toxic symptoms have been observed which include sensations of a "band around the head," nausea, and perspiration. Effects are apparent within ten minutes and last less than two hours. One of 4 patients reported seeing spots of color on the wall. We are still gradually increasing the dose.

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We have been asked by Doctor Kety of the National Institute of Mental Health to study the effects of this crude drug. Preliminary exploration is now going on. Doses of 0.8 gram of the ground seeds (approximately 20 seeds) caused no discernible effect other than subjective reports of blurred vision in 2 of 4 patients. We are continuing to increase the dose gradually and will report if any striking results are obtained.

NEUROSURGICAL PROJECT AT THE NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, NIH.

I have discussed this project with Doctor Wikler. It has been proposed to study the effects of drugs on perceptual tracts, pathways, and responses using neurosurgical patients in whom cortical exploration and extirpation is carried out for epilepsy. Both Dr. Wikler and myself believe that this would be a very important project which would have great theoretical significance. It is certainly worthy of support, but neither of us are in any position to advise as to whether or not it can be supported financially.

Sincerely yours,

Harris Isbell

Harris Isbell, M.D.
Director

HI:rn:lw

Enclosures: 3 Tables.
Copy of Proj. Description
f.y. 1957.

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EFFECTS OF COMBINATIONS OF HYOSCINE AND LSD

sure	Placebo-Placebo	Placebo-LSD	0.42 mg. Hyoscine	0.42 mg. Hyoscine + LSD	0.64 mg. Hyoscine + LSD	0.85 mg. Hyoscine + LSD	Placebo-Placebo	Placebo-LSD	1.3 mg. Hyoscine	1.3 mg. Hyoscine + LSD
e rk	+ 0.61	+ 2.59*	+ 0.51	+ 2.73*	+ 3.30*	+ 2.46*	+ 0.83	+ 3.08*	+ 1.44**	+ 3.26*
l ly ze	+ 1.10	+ 3.51*	+ 1.15	+ 3.87*	+ 4.36*	+ 4.24**	+ 0.54	+ 3.45*	+ 2.00*	+ 4.65**
olic d sure	+ 1.03	+ 2.29*	+ 0.19*	+ 1.48*	+ 1.37**	+ 1.19**	+ 0.73	+ 2.00*	- 0.51**	+ 0.43**
er of sitive swers	10	88*	29*	88*	106**	114**	10	65*	42*	116**
nical ade	0	1.22*	0	1.22*	1.5*	1.6*	0.05*	1.1*	0.4*	1.5*

Experiments to left of double line, means of observations on 11 patients; to right, means of 12 patients.

* Significantly different from placebo-placebo
** Significantly different from placebo-LSD

EFFECTS OF COMBINING 20 mg. DL AMPHETAMINE WITH 60 mcgm. LSD

Measure	Placebo-Placebo	Placebo-LSD	Placebo-Amphetamine	Amphetamine-LSD
Knee Jerk	± 1.21	± 2.88*	± 1.13	± 3.24*
Pupillary Size	± 0.48	± 4.20*	± 1.00	± 3.98*
Systolic Blood Pressure	± 0.92	± 2.98*	± 2.74	± 4.77**
Number of Positive Answers	12	84*	21	98*
Clinical Grade	0.14	1.4*	0.18	1.18*

All figures are means on 11 subjects.

Knee jerk, pupillary size, and systolic blood pressure expressed as area under time-action curve during first 8 hours after administration of LSD. Clinical grades on basis of 1 - 4.

* Statistically significant from placebo-placebo.

** Statistically significant from placebo-LSD.

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EFFECT OF RESERPINE ON INTENSITY OF LSD REACTION

asure	Placebo + Placebo	Reserpine[4] + LSD Placebo	Placebo + LSD[5]	Reserpine[4] 5.0 mg "O" + LSD[5]	Reserpine[6] 7.5 mg "O" + LSD[5]	Reserpine[7] 6.0 mg I.M. + LSD[5]
ee Jerk[1]	±0.27 ±0.34	±0.5 ±0.36	±2.72 ±0.53	±2.95 ±0.4	±3.47 ±0.33	±3.33 ±0.27
pillary[1] ze	-0.11 ± 0.4	-0.96 ±0.39	±3.85 ±0.56	±3.33 ±0.44	±3.82 ±0.28	±3.35 ±0.33
stolic[1] ood essure	±0.91 ±0.4	±0.76 ±0.36	±2.54 ±0.54	±2.07 ±0.68	±2.15 ±0.36	±1.81 ±0.49
mber[2] sitive swers	18 ±8	33 ±10	121 ±20	110 ±22	120 ±24	163 ±30
inical[3] ade	0	0	2.25 ±0.28	2.37 ±0.27	2.17 ±0.3	2.5 ±0.7

Figures represent mean area ± standard errors under time-action curve and are means of values on 12 subjects.

presents means of counts ± standard errors of number of positive answers after LSD was given.

Based on rating scale of 0-4.

2.5 mg. orally 10 and 2 hours prior to LSD.

75 mcg. orally.

2.5 mg. orally 22, 10 and 2 hours prior to LSD.

2.0 mg. intramuscularly 22, 10 and 2 hours prior to LSD.